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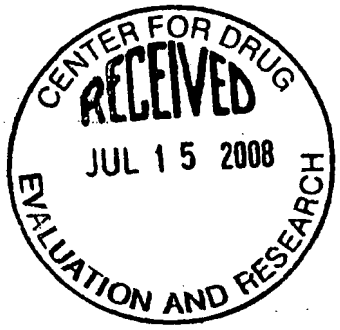

Dockets Management Branch
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fisher Lane, Room 1061
Rockville, MD 20852

Re: Request for Revision of Regulatory Review Period
ZOLINZA® (vorinostat)
Docket No. 2007E-0143

Dear Sir or Madam:

Merck & Co., Inc. ("Merck"), successor to Aton Pharma, along with Sloan-Kettering Institute for Cancer Research ("Sloan-Kettering") and the Trustees of Columbia University in the City of New York ("Columbia University"), through undersigned counsel, hereby requests reconsideration and revision of the Determination of Regulatory Review Period published in the Federal Register on May 14, 2008 (Fed. Reg. Vol. 73, No. 94 at 37838-39). In accordance with 21 C.F.R. § 60.24(a), the following information is provided:

(1) The Type of Action Requested

For the reasons stated below, Applicant respectfully requests that (1) the "date the application was initially submitted with respect to the drug product under section 505(b) of the act" be corrected from April 7, 2006, the date provided in the Federal Register notice, to December 6, 2005; and (2) the "date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i)

became effective" be corrected from January 24, 2000, the date provided in the Federal Register notice, to October 2, 1999. Applicant also requests that the agency recalculate the "regulatory review period" accordingly.

(2) The Identity of the Product

ZOLINZA® (NDA 21-991), the product that is the subject of the regulatory review period determination, is marketed and sold by Merck.

(3) The Identity of the Applicant

Sloan-Kettering and Columbia University were the initial applicants on the Request for Extension of Patent Term. Sloan-Kettering and Columbia University exclusively licensed the rights to the patent at issue to Aton Pharma. The rights are now exclusively licensed to Merck as a result of Merck's acquisition of Aton Pharma.

(4) The FDA Docket Number

The FDA Docket Number for this Determination of Regulatory Review Period is 2007E-0143.

(5) The Basis for the Request for Revision, Including Any Documentary Evidence

Aton Pharma submitted the initial component of the New Drug Application ("NDA") for ZOLINZA® on December 6, 2005. The Center for Drug Evaluation and Research ("CDER") of the Food and Drug Administration ("FDA") began reviewing that information shortly thereafter. Therefore, December 6, 2005 -- not any later date -- is the date on which the application was "initially submitted" to FDA for purposes of the Drug Price Competition and Patent Term Restoration Act of 1988

("DPC/PTR Act").[1] As shown below, this conclusion is consistent with the statute, congressional intent, and FDA's implementing regulations.

Also, Sloan-Kettering submitted the Investigational New Drug Application ("IND") for ZOLINZA® on September 2, 1999, and the IND became effective on October 2, 1999. CDER placed a clinical hold on the IND on October 5, 1999. Sloan-Kettering worked diligently to resolve FDA's concerns about the clinical study. The clinical hold was removed on January 24, 2000. Therefore, October 2, 1999, not January 24, 2000, is the date that the IND became effective.

Documentary evidence supporting this request for revision is provided in Exhibits A through E hereto. In addition, the discussion below includes references to documents in FDA's files.

I. AN NDA IS INITIALLY SUBMITTED WHEN FDA HAS SUFFICIENT INFORMATION TO COMMENCE REVIEW

A. LEGISLATIVE FRAMEWORK

1. The Statute Provides That the Approval Phase Begins When an Application Is "Initially Submitted."

The DPC/PTR Act permits drug innovators to extend the patent life of a drug in order to recover a portion of the drug's patent life lost during FDA marketing approval.[2] Congress recognized that "although the patent term in the United States is 17 years, the period during the patent term in which products are marketed (the effective patent term) is usually less than 17 years because patents often are obtained before

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1 Pub. L. No. 98-417, 98 Stat. 1585 (1984).

2 Pub. L. No. 98-417, 98 Stat. 1585 (1984).

products are ready to be marketed."[3] Congress intended the DPC/PTR Act to stimulate research and development of new drugs by restoring patent life lost during FDA-required testing and review, thereby allowing developers of new drugs to recoup more of their research and development costs.[4]

The DPC/PTR Act provides that the term of a patent for a new drug product may be extended for up to five years if, prior to marketing, the product was subject to regulatory review by FDA.[5] It is necessary to calculate the "regulatory review period" to determine the length of the patent term extension. For a new drug, this period covers time consumed by two phases that typically occur during the life of the patent and substantially reduce the time the drug may be marketed while subject to patent protection. The first phase (the "testing phase") begins on the date "an exemption under subsection (i) of section 505 or subsection (d) of section 507 became effective for the approved human drug product" and ends "on the date an application was *initially submitted* for such drug product under section 351, 505, or 507."[6] The second phase (the "approval phase") begins "on the date the application was *initially submitted* for the approved

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3 H. R. Rep. No. 98-857, pt. 1, at 17 (1984).

4 130 Cong. Rec. 10989 (1984) (statement of Sen. Hatch); 130 Cong. Rec. 8706 (1984) (statement of Rep. Waxman).

5 Pub. L. No. 98-417, 98 Stat. 1585 (1984).

6 35 U.S.C. § 156(g)(1)(B)(i) (emphasis added). FDA regulations refer to this period as the "testing phase." 21 C.F.R. § 60.22. The regulations explain that "[t]he testing phase begins on the date an exemption under section 505(i) of the [Federal Food, Drug and Cosmetic Act ("FDCA")] become effective . . . for the approved human drug product and ends on the date a marketing application under section 351 of the Public Health Service Act or section 505 of the [FDCA] is initially submitted to FDA." 21 C.F.R. § 60.22(a)(1). The patent term may be extended by one-half of the time a new drug is in the testing phase. *See* 35 U.S.C. § 156(c)(2).

product under section 351, subsection (b) of section 505, or section 507" and ends "on the date such application was approved under such section."[7]

Congress was particularly concerned with the restoration of patent rights to make up for time lost during FDA's review of an application. While Congress provided for only 50 percent restoration of time spent during the testing phase, it ensured that full credit was given for the approval phase, when FDA review was ongoing.

2. The Legislative History Makes Clear That an Application Is "Initially Submitted" When FDA Has Sufficient Information to Commence Review.

Congress intended that, for purposes of computing restoration of patent life, the approval phase would begin at the point when FDA has received enough information to begin review. The legislative history shows that Congress deliberately chose the words "initially submitted" to identify the end of the testing phase and the commencement of the approval phase, explicitly distinguishing that moment from a later point in time when an application is considered "filed." The House Report accompanying the DPC/PTR Act notes that in the definition of the "regulatory review period,"

> the term "initially submitted" is used to describe the point in time when the testing phase is considered to be completed and the agency approval phase to have begun. This term is used instead of the term "filed," because an application is often not considered to be filed, *even though*

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[7] 35 U.S.C. § 156(g)(1)(B)(ii) (emphasis added). FDA regulations refer to this period as the "approval phase." 21 C.F.R. § 60.22.

The patent term may be extended for as many days as the new drug was in the approval phase. For a patent issued after the enactment of the DPC/PTR Act, however, the period of extension may not exceed five years. *See* 35 U.S.C. § 156(g)(6)(A). In addition, the patent term may not extend beyond 14 years after the date of approval. *See* 35 U.S.C. § 156(c)(3).

> *agency review has begun*, until the agency has determined that no other information is needed and a decision on the application can be made. For purposes of determining the regulatory review period and its component periods, an application for agency review is considered to be "initially submitted" if the applicant has made a deliberate effort to submit an application containing all information necessary for agency review to begin. The Committee recognizes that the agency receiving the application might decide it needs additional information or other changes in the application. *As long as the application was complete enough so that agency action could be commenced, it would be considered to be "initially submitted."*[8]

Thus, the approval phase begins when the new drug applicant has submitted enough information for FDA to begin its review. This makes sense because the amount of patent life consumed by FDA's review of the marketing application depends on when FDA *begins* its review of the application. Importantly, the House Report states that an application is considered "initially submitted" when the materials submitted are complete enough that the agency can commence review, *not* when an applicant has submitted all components of the application. Congress plainly intended that an application would be considered "initially submitted" when FDA has enough information to begin the review process, even if the application is not yet complete or "filed."

B. REGULATORY FRAMEWORK

1. FDA Regulations State That a New Drug Application Is "Initially Submitted" When the Applicant Provides Sufficient Information for the Agency to Commence Review.

FDA's regulations implementing the DPC/PTR Act are consistent with the language and legislative history of the statute, providing that the approval phase begins

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[8] H. R. Rep. No. 98-857, pt. 1, at 44 (1984) (emphasis added).

when FDA has sufficient information to commence review of the application. The regulations state that "[t]he approval phase begins on the date a marketing application under section 351 of the Public Health Service Act or section 505(b) of the [FDCA] is *initially submitted* to FDA . . . and ends on the date the application is approved."[9] They go on to explain that, "[f]or purposes of determining the regulatory review period for any product, a marketing application . . . is *initially submitted* on the date it contains sufficient information *to allow FDA to commence review* of the application."[10] Thus, if an applicant has provided FDA with sufficient information regarding a substantial element of an application, so that the agency is in a position to commence review of the application, the approval phase begins.

2. New Drug Applicants May Elect a Fast Track Review Process.

In the case of new drugs, the timing of FDA review will depend on the choice of review process. FDA has two independent tracks for approval of an NDA. Under the traditional review process, CDER will not accept and review separate submissions of individual components of an NDA.[11] Rather, the agency begins review only upon receipt of the entire NDA.

FDA provides an alternative method of review for applications to market new drugs. New drug applicants may elect to have the agency conduct a "fast track review" of an NDA. A new drug is eligible for fast track review if the product is intended for the treatment of a serious or life-threatening condition and demonstrates the

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9 21 C.F.R. § 60.22(a)(2) (emphasis added).

10 21 C.F.R. § 60.22(f) (emphasis added).

11 *See* 21 C.F.R. § 314.50; *see also* 21 C.F.R. § 314.101(a)(2).

potential to address unmet medical needs for the condition.[12] If FDA determines that an application may be fast-tracked, "the Secretary shall evaluate for filing, and may commence review of portions of, an application for the approval of the product before the sponsor submits a complete application."[13] Thus, fast track review status permits a manufacturer to submit portions of a marketing application to CDER for "rolling review."[14] CDER will accept for submission only a complete section or "reviewable unit" of the application.[15] Upon receipt of the application data, CDER may begin reviewing the submission even if other sections have not yet been submitted. CDER may notify the applicant of its conclusions regarding the data submitted with a particular section. A final decision approving an application is issued only after the applicant submits and FDA reviews every section of the application.

3. A Fast Track Review Application Is "Initially Submitted" Long Before Formal Submission of the Administrative NDA.

When a new drug application is submitted under the fast track review process, the application is "initially submitted" long before the submission of the final section of the NDA. FDA may begin its review with the submission of the first technical

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12 21 U.S.C. § 356(a)(1).

13 21 U.S.C. § 356(c)(1).

14 21 U.S.C. § 356(c); *see also* S. Rep. No. 105-43 at 43 (1997) (Noting that fast track applications are eligible for "rolling review.").

15 "Occasionally, the Agency may, in its discretion, accept less than a complete section (e.g., a CMC section lacking final consistency lot data and long term stability data; an acute toxicology section lacking chronic toxicology data; or final study reports for some or all of the principal controlled trials without integrated summaries) if it determines that such a subsection would constitute a reviewable unit and would be useful in making the review process more efficient overall." FDA, Guidance for Industry: Fast Track Drug Development Programs - Designation, Development, and Application Review (Jan. 2006) at p. 13-14.

section supporting a fast track application, rather than waiting until all sections have been submitted. So long as the first submission contains sufficient information for CDER to begin a meaningful review, the application has been "initially submitted" and the approval process has begun.

CDER itself describes the process in these terms. The agency's guidance document states that CDER will only accept a portion of an application if submission is sufficient to commence review of the application.[16] Thus, in the fast track review process, substantive review may begin before the submission of all sections of the application.

Any conclusion that an application handled through the fast track review process has been "initially submitted" only when all sections of the application have been submitted and reviewed would be wholly inconsistent with congressional intent. Congress wanted to restore the full amount of time consumed by FDA review of a marketing application. As discussed above, in explaining its choice of the words "initially submitted" to define the beginning of the approval phase, Congress explicitly distinguished between submission of enough information to allow agency review to begin and the formal step of "filing," which may occur only after an application is complete. Congress made clear that it was choosing the earlier point as the beginning of the approval phase. Under the fast track review process, much of this review (consuming several months in this case) occurs before filing of the last section of an NDA. Re-defining the approval phase to encompass only the short period needed to review the final

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[16] FDA, Guidance for Industry: Fast Track Drug Development Programs - Designation, Development, and Application Review (Jan. 2006) at p. 13-14.

section of an NDA would deprive the applicant of full credit for the time consumed by FDA's review, contrary to Congress's intent.

In several cases, FDA has concluded that a new drug application was "initially submitted" only at the point when the applicant formally submitted a complete application.[17] This case is clearly distinguishable, since these other cases did not involve a rolling submission that triggered commencement of FDA review. In fact, FDA's reasoning in Docket No. 91E-0491 supports Applicant's argument here. In that docket, FDA apparently acknowledged that an application could be "initially submitted" before it was formally filed. The critical fact in that case was that the applicant there had not submitted enough information for FDA to begin its review.

As described above, when an applicant requests and FDA grants fast track review, the agency's review may begin long before an application is complete. FDA can comply with Congress's intent to grant full credit for the period consumed by agency review only if it finds that the application is "initially submitted" when the applicant submits the first round of information in support of the application.

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[17] In Docket No. 91E-0491, FDA concluded that an "incomplete application" submitted by Sankyo and Bristol-Myers Squibb did not contain sufficient information to permit FDA to commence review, despite the fact that FDA staff had made inquiries about information in the application. The agency concluded that the application was not "initially submitted" where the submission did not include all information the agency had required in presubmission communications with the applicant. *See* Letter from Stuart L. Nightingale, M.D., Associate Commissioner for Health Affairs, FDA, to Terry Coleman, Esq., Fox, Bennett & Turner (March 1, 1994), *available in* FDA Docket No. 91E-0491. *See also Aktiebolaget Astra v. Lehman*, 71 F.3d 1578, 1578-79 (Fed. Cir. 1995) (noting FDA's decision that an "early" submission of information did not start the review period clock and that Astra's approval stage began only when the company filed the last component of its NDA).

II. CALCULATION OF THE REGULATORY REVIEW PERIOD FOR ZOLINZA® PATENT EXTENSION

The patent for which extension is sought is Patent No. RE38,506E, which issued on April 20, 2004. The patent is a reissue of Patent No. 5,369,108, which issued on November 29, 1994. In September 1999, Aton Pharma requested establishment of IND 58,915 to investigate the use of its proprietary suberoylanilide hydroxamic acid, vorinostat. When taken orally, vorinstat is indicated for treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistant or recurrent disease on or following two systemic therapies.

Merck eventually assumed responsibility for this approval process. In December 2005, Merck filed an application for marketing approval for vorinostat, known as ZOLINZA®. FDA granted approval of the marketing application on October 6, 2006.

A. THE NDA WAS INITIALLY SUBMITTED ON DECEMBER 6, 2005.

1. FDA Used the Fast Track Review Process for the ZOLINZA® Marketing Application.

FDA reviewed the marketing application for ZOLINZA® under the fast track review process. Each component of the application was submitted separately, referencing the fast track review procedure. The first component to be submitted for review, the Nonclinical Section, was submitted on December 6, 2005. The CMC Section followed on February 22, 2006, and the Clinical Section and Module 1 on April 5, 2006,[18] completing the application. On May 31, 2006, FDA stated that the NDA was

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[18] In its regulatory review determination, the agency states that the final module of the NDA was submitted on April 7, 2006. That submission is dated April 5, 2006, however, and in contemporaneous correspondence, FDA refers to the "April 5, 2006 new drug

sufficiently complete to permit a substantive review. On October 6, 2006, FDA issued an approval letter for ZOLINZA®.

2. The Application for ZOLINZA® Was "Initially Submitted" on December 6, 2005.

The marketing application for ZOLINZA® was "initially submitted" to FDA on December 6, 2005, when the Nonclinical section of the application was submitted to the agency. At that point there was "sufficient information to allow FDA to commence review of the application."[19]

As early as the pre-NDA meeting communications, FDA made clear that it planned to review sections of the NDA on a rolling basis as the agency received them. In correspondence beginning in November 2005, for example, FDA requested that each module and associated information be ready for review at the time of module submission. For example, in connection with the Chemistry review, the agency requested that Applicant confirm that "all referenced Drug Master Files are updated and ready for review at the time of the Quality unit submission."[20] The agency further recommended that Applicant submit a new Drug Master File "in advance of the NDA chemistry section."[21] In accordance with the agency's recommendation, Applicant responded with

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application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zolinza (vorinostat) Capsules, 100 mg." Letter to Randi Albin, Ph.D., Director, Regulatory Affairs, Merck & Co., Inc., from Paul Zimmerman, Project Manager, Division of Oncology Products, Office of Oncology Drug Products, Center for Drug Evaluation and Research, FDA (May 31, 2006) (Attached as Exhibit A).

19 21 C.F.R. § 60.22(f).

20 Email from Ann Staten, U.S. Food and Drug Administration, to Randi Albin, Merck (Jan. 5, 2006 12:35 PM) (attached as Exhibit B).

21 *Id.*

a plan for the new Drug Master File to be filed "in January 2006, in advance of the February 22, 2006 submission date for the NDA chemistry section."[22]

In short, FDA's own correspondence makes plain that, in accordance with the agency's requests, Applicant constructed each section of the NDA it submitted on a rolling basis so as to permit the agency to begin substantive review of that section immediately. FDA's conclusion that the ZOLINZA® application was "initially submitted" on April 7, 2006, the date the final section of the NDA was filed, is inconsistent with FDA's own requests, and with the governing regulations, because the December 6, 2005 filing was sufficient to allow CDER to begin a substantive review. Moreover, FDA's determination here disregards Congress's deliberate decision to pick a date different from (and earlier than) the official "filing" date as the beginning of the approval phase, to be certain that applicants would obtain full credit for the time lost as a result of FDA review.

FDA's conclusion that the ZOLINZA® application was "initially submitted" on April 7, 2006 rather than December 6, 2005, also has the result of depriving Merck of full credit for four months of the time when FDA was conducting its review of the various components of the application. The effect of this determination is that these months will be classified as part of the testing phase, and only half of that time is restored to the patent term. This result is directly contrary to Congress's intent that applicants receive full credit for the period of FDA review.

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22 *Id.*

Applicant was clearly diligent in submitting information for review and otherwise pushing the approval process forward. Within a few months of the initial submission, it submitted the balance of the application (with the CMC section going in on February 22, 2006) and submitted the final section in April 2006.[23] Fast track review worked exactly as it should have, with the agency well along in its review of the application when the final section was submitted, and there is no basis for concluding that the ZOLINZA® application was "initially submitted" on any date other than the date when the first component was submitted. FDA should grant full credit for the review and approval period by determining that the application was "initially submitted" on December 6, 2005.

B. The IND Became Effective on October 2, 1999.

Sloan-Kettering's IND for ZOLINZA® became effective on October 2, 1999, because FDA did not place an effective hold on the application until October 5, 1999. Under FDA regulations, an IND becomes effective "[t]hirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold."[24] Sloan-Kettering submitted the IND for ZOLINZA® to FDA on September 2, 1999.[25] FDA received the application on September 3, 1999.[26]

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[23] Letter to Randi Albin, Ph.D., Director, Regulatory Affairs, Merck & Co., Inc., from Paul Zimmerman, Project Manager, Division of Oncology Products, Office of Oncology Drug Products, Center for Drug Evaluation and Research, FDA (May 31, 2006) (Attached as Exhibit A).

[24] 21 C.F.R. 312.40(b)(1).

[25] Letter to Francis M. Sirotnak, Memorial Sloan-Kettering Cancer Center, from Dotti Pease, Chief, Project Management Staff, Division of Oncology Drug Products, Center for Drug Evaluation and Research, FDA (Sept. 13, 1999) (Attached as Exhibit C).

[26] *Id.*

FDA did not place an effective hold on the clinical study until October 5, 1999. The agency's regulations state that a clinical hold order "will be made by or on behalf of the Division Director with responsibility for the IND."[27] Sloan-Kettering was not notified of a clinical hold order "by or on behalf of the Division Director" until the October 5, 1999 letter.[28] Sloan-Kettering then worked diligently to address the issues raised in the letter, and FDA removed the clinical hold on January 24, 2000.[29] The agency's communications with Sloan-Kettering prior to the October 5 letter did not state that a clinical hold order had been issued by or on behalf of the Division Director and therefore did not constitute an effective clinical hold preventing the IND from going into effect. Therefore, the IND for ZOLINZA® became effective on October 2, 1999; 30 days after Sloan-Kettering submitted the application to FDA.

C. The Regulatory Review Period for ZOLINZA®.

The investigational new drug application for ZOLINZA® became effective on October 2, 1999. As explained above, the marketing application for ZOLINZA® was "initially submitted" to FDA on December 6, 2005. FDA approved the marketing application for ZOLINZA® on October 6, 2006.

The testing phase for ZOLINZA® is the time between the effective date of the investigational new drug application and the date the marketing application was

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[27] 21 C.F.R. 312.43(d).

[28] Letter to Francis M. Sirotnak, Memorial Sloan-Kettering Cancer Center, from Richard Pazdur, M.D., Director, Division of Oncology Drug Products, Center for Drug Evaluation and Research, FDA (Oct. 5, 1999) (Attached as Exhibit D).

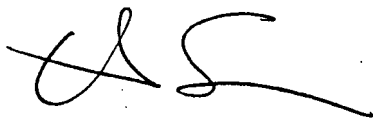
[29] Letter to Francis M. Sirotnak, Memorial Sloan-Kettering Cancer Center, from Richard Pazdur, M.D., Director, Division of Oncology Drug Products, Center for Drug Evaluation and Research, FDA (Jan. 24, 2000) (Attached as Exhibit E).

"initially submitted" -- a total of 2258 days. The approval phase began when the applicant "initially submitted" the marketing application and ended on the date that FDA approved the marketing application. Thus, the length of the approval phase for ZOLINZA® was 304 days.

CONCLUSION

For the reasons discussed above, FDA's determination of the regulatory review period for ZOLINZA® is incorrect. The agency should revise the determination to reflect that the application was "initially submitted" on December 6, 2005, and that the approval phase of the regulatory review period began on that date. Also, the agency should revise the determination to reflect that the IND became effective on October 2, 1999, and that the testing phase began on that date.

Respectfully submitted,



Christopher N. Sipes
Attorney for Merck & Co., Inc.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-991

Merck & Co., Inc.
Attention: Randi Albin, Ph.D.
Director, Regulatory Affairs
P.O. Box 2000
RY32-605
Rahway, NJ 07065

Dear Dr. Albin:

Please refer to your April 5, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zolinza (vorinostat) Capsules, 100 mg.

We also refer to your submissions dated December 6, 2005 and February 22, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on June 6, 2006 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Paul Zimmerman, Project Manager, at (301) 796-1489.

Sincerely,

{See appended electronic signature page}

Paul Zimmerman
Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Dr. Randi Albin
JUN - 5 2006

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Zimmerman
5/31/2006 10:35:57 AM

Moody, Christopher

From: Staten, Ann M [STATENA@cder.fda.gov]
Sent: Thursday, January 05, 2006 12:35 PM
To: Albin, Randi L
Subject: RE: PreNDA meeting responses

Dear Randi,

Thank you for your patience on this one. We have the following response to your below e-mail.

> *Merck & Co., Inc., and its contracted manufacturers of the drug substance and drug product for this application (Organichem, Inc., and Patheon, Inc., respectively) will be ready for a preapproval inspection at the time of completion of filing of the rolling NDA (April 12, 2006).*
>
> **FDA Comment: It is acceptable for sites to be ready for inspection at the time of complete filing for the NDA.**
>
> *Is the April 12, 2006 preapproval inspection date for the drug substance and drug product manufacturing sites acceptable to the Chemistry reviewer(s)?*
>
> **FDA Response: Please contact the appropriate FDA district and/or Office of Compliance regarding this question. Confirmation of a specific pre-approval inspection date cannot be provided by the Chemistry Reviewer(s).**

I will try to call you today.

Sincerely,
Ann

> -----Original Message-----
> **From:** Albin, Randi L [mailto:randi_albin@merck.com]
> **Sent:** Thursday, December 08, 2005 4:49 PM
> **To:** Staten, Ann M
> **Subject:** RE: PreNDA meeting responses
>
> Dear Ann,
>
> This e-mail provides MRL's response to the e-mail communications from the Agency dated November 30, 2005 and December 5, 2005 that provided answers and comments to the questions presented in the pre-NDA background package. I have provided the original question posed by MRL followed by the FDA response and comment in bold-face. Our response to the comments is provided in italicized text.
>
> - In accordance with provisions of the Fast Track regulations, does the Agency concur with the proposed timeline to roll out Module 4 (Nonclinical Study Reports, including the Nonclinical Overview and Nonclinical Written Tabulated Summaries) and Module 3 (Quality, including quality Overall Summary) components of the planned NDA for vorinostat as described above?
>
> **FDA Response: Yes.**
>
> **Chemistry: The proposed timeline and submission date of 22-FEB-2006 are acceptable. Please ensure that all drug substance and drug product manufacturing sites are ready for inspection at the time of the Quality unit submission. Also confirm that all referenced Drug Master Files are updated and ready for review at the time of the Quality unit submission.**
>
> *MRL Response: The referenced Drug Master files will be updated and ready for review at the time of the Quality unit submission (February 22, 2006). Please see additional response below.*

Merck & Co., Inc., and its contracted manufacturers of the drug substance and drug product for this application (Organichem, Inc., and Patheon, Inc., respectively) will be ready for a preapproval inspection at the time of completion of filing of the rolling NDA (April 12, 2006).

Is the April 12, 2006 preapproval inspection date for the drug substance and drug product manufacturing sites acceptable to the Chemistry reviewer(s)?

Clinical Pharmacology: Please provide a list of completed and ongoing clinical pharmacology and biopharmaceutical studies.

MRL Response: To provide supportive biopharmaceutical data, we are presently conducting a single study, "A Phase I Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Vorinostat in Patients With Advanced Cancer". The protocol for this study (Protocol No. 008) was submitted to the IND on July 7, 2004 (Serial No. 107). The study is comprised of two parts (Part I and Part II), the first of which has been completed. In Part I of the study, pharmacokinetic data (serum and urine) of the parent compound and inactive metabolites were collected following administration of vorinostat at a dose of 400 mg administered once daily. Single-dose and multiple-dose pharmacokinetic samples were collected, and the effect of a high-fat meal was assessed. Part II of the study will collect additional safety and pharmacokinetic data for vorinostat when administered at a different dose and schedule.

The results of Part I will be included as a CSR in the NDA. Part II of the study will initiate in 1Q06.

* Does the proposed Table of Contents for Module 3 fulfill the requirements of the Agency reviewer(s)?
FDA Response: See comments above in response to question #1. The proposed Table of Contents is acceptable. Additionally, the Agency recommends that the new Drug Master File be submitted in advance of the NDA chemistry section. This will ensure the appropriate processing time for assignment of DMF number and immediate reviewer access, upon submission of the NDA.

MRL Response: Organichem, Inc. is planning to file the Drug Master File for vorinostat in January 2006, in advance of the February 22, 2006 submission date for the NDA chemistry section.

Additional CMC comments:

1. **Please confirm the date of USAN adoption for the drug's established name. If the date of adoption is very recent, the inclusion of the appropriate correspondence in the NDA is recommended.**

MRL Response: The date of USAN adoption for the drug's established name was April 27, 2005. Notification of USAN Council approval of the generic name was submitted to the IND on May 25, 2005 (Serial No. 180). The statement on a nonproprietary name adopted by the USAN Council was posted to the www.ama-assn.org website on June 27, 2005. Vorinostat was included in the listing of USAN released for publication in 2005 on November 7, 2005.

2. **Any stability updates should be submitted no later than two months prior to the submission's PDUFA date.**

MRL Response: Any stability updates will be submitted no later than two months prior to the submission's PDUFA date.

* Does the Agency agree with the proposal to include the body diagram work sheets for each patient in the Appendix to the CSR for Protocol 001 with the supportive digital photographs?

FDA Response: Yes. However, digital photographs should be submitted as .pdf files

MRL Response: The supportive digital photographs that will be included in the CSR for Protocol 001 will be submitted as .pdf files.

* **Additional FDA Comments:**

1. **Please make sure that you include the individual investigator site, address and contact information.**

   DSI Reviewer: We will need the contact information from each study site (i.e., name of clinical investigator, address, phone number, and fax number) included somewhere in the NDA submission.

   MRL Response: For all studies included in the NDA that will be accompanied by a CSR, contact information for each study site will be included in the NDA.

2. **Statistical Comment: Please include in your submission (a) SAS programs that produced all efficacy results, (b) all raw as well as derived variables in .xpt format, (c) SAS programs by which the derived variables were produced from the raw variables. For example, the SAS program(s) for deriving response status (such as CR, PR SD, PD) from original individual tumor measurements.**

   MRL Response: All raw and derived variables (in .xpt format) along with all the SAS programs for generating the derived variables and for generating the statistical tables will be provided.

3. **The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.**

   MRL Response: The proposed proprietary name and all associated labels and labeling will be submitted to the Agency as soon as available.

In order to consolidate the Agency's comments with our responses, I plan to follow-up this e-mail with a written letter that will be submitted to IND 58,915 as a General Correspondence. We thank the Division for its feedback on our submission plans. Please let me know if we can provide any additional clarification.

Sincerely,
Randi

Randi Albin, Ph.D.
Director
Regulatory Affairs
Merck & Co. Inc.
RY32-605
P.O. Box 2000
Rahway, NJ 07065
Ph: 732-594-4240
Fax: 732-594-1030
e-mail: randi_albin@merck.com

-----Original Message-----
From: Staten, Ann M [mailto:STATENA@cder.fda.gov]
Sent: Monday, December 05, 2005 8:23 AM
To: Albin, Randi L.
Subject: RE: PreNDA meeting responses

Dear Randi,

Here is a comment that the DSI reviewer will want to see in the NDA. Hopefully, it will be easy to include and easy to locate.

> We will need the contact information from each study site (i.e., name of clinical investigator, address, phone number, and fax number) included somewhere in the NDA submission.

Thanks,

Ann

> -----Original Message-----
> **From:** Albin, Randi L [mailto:randi_albin@merck.com]
> **Sent:** Thursday, December 01, 2005 11:32 AM
> **To:** Staten, Ann M
> **Subject:** RE: PreNDA meeting responses
>
> Dear Ann,
>
> Thank you for providing the FDA answers to the questions submitted with our pre-NDA background package for vorinostat. As these answers are clear to us, and as we discussed in our telephone conversation this morning, we respectfully request that the Type B meeting scheduled for December 5, 2005 be cancelled.
>
> We will be providing responses to the Chemistry and Clinical Pharmacology comments as well as the additional CMC and FDA comments in a separate communication. I hope to be able to provide you with these next week.
>
> Regards,
> *Randi*
>
> Randi Albin, Ph.D.
> Director
> Regulatory Affairs
> Merck & Co. Inc.
> RY32-605
> Rahway, NJ 07065
> Ph: 732-594-4240
> Fax: 732-594-1030
> e-mail: randi_albin@merck.com

> -----Original Message-----
> **From:** Staten, Ann M [mailto:STATENA@cder.fda.gov]
> **Sent:** Wednesday, November 30, 2005 2:09 PM
> **To:** Staten, Ann M; Albin, Randi L
> **Subject:** PreNDA meeting responses

Hi Randi,

Attached are the FDA answers to your questions. You have the option of canceling our meeting of 12-5-05 if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible if you are canceling the meeting.

Sincerely,
Ann

<<preNDA Agenda Items and Issues for Discussion.doc>> <<PRE-NDA MEETING BULLETS.doc>>

****

Ann Staten, RD
CDR, United States Public Health Service
Food and Drug Administration
Division of Drug Oncology Products
ph: 301.796.1468
fax: 301.796.9867

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"EMF <fda.hhs.gov>" made the following annotations.

DEPARTMENT OF HEALTH & HUMAN SERVICES

FDA C
IND 58,915
CO: 279938

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 58,915

SEP 13 1999

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10021

Atten: Francis M. Sirotnak, Ph.D.

Dear Dr. Sirotnak:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 58,915

Sponsor: Memorial Sloan-Kettering Cancer Center

Name of Drug: Suberoylanilide Hydroxamic Acid/SAHA

Date of Submission: September 2, 1999

Date of Receipt: September 3, 1999

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information (21 CFR 312.32 (c)(2)); (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days of initial receipt of the information (21 CFR 312.32 (c)(1)); and (3)

submitting annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

(if via U.S. Postal Service)

FDA/CDER
Division of Oncology Drug Products
HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

(if via courier)

FDA/CDER
Division of Oncology Drug Products
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852

Should you have any questions concerning this submission, please contact: Ann Staten (301) 594-5770

Sincerely yours,

Ann Staten

for Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center of Drug Evaluation and Research

cc:
Original IND 58,915
HFD-150/Div. Files
HFD-150/CSO/

filename: C:\WPWIN61\TEMPLATE\FDA\I58915.WPD

IND ACKNOWLEDGEMENT

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 58,915

OCT 15 1999

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10021

Attention: Francis M. Sirotnak, Ph.D.

Dear Dr. Sirotnak:

Please refer to your Investigational New Drug Application (IND) submitted September 2, 1999, received September 3, 1999, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for suberoylanilide hydroxamic acid (SAHA).

We also refer to the October 1, 1999, telephone conversation between Madeline Tappert of your office and Ann Staten, Project Manager of this Division in which you were notified that the study you proposed is on clinical hold and may not be initiated because deficiencies under 21 CFR 312.42(b)(1)(i) lead us to conclude that the study may pose an unreasonable and significant risk of illness or injury to human subjects. Summarized below is the specific deficiency and the information needed to resolve the deficiency.

Toxicology studies in a rodent and a non-rodent using the same route, schedule and duration of administration as the intended treatment cycle are typically provided to support Phase 1 trials of oncology drugs (*Cancer Chemother. Pharmacol.*, 41:173-185, 1998). In addition, at least one of these studies is expected to provide a histopathology examination at doses that cause toxicity. The single dose animal studies you have provided are inadequate to address the safety of the daily x 5 schedule in humans, because they do not address the potential cumulative or schedule dependent toxicity of SAHA. Furthermore, since no histopathology data were provided, these studies are also inadequate to support a single dose trial of SAHA.

The following two studies together would be sufficient to allow a daily x 5 study to proceed in humans:

1. A daily x 5 toxicology study in rodents that provides a determination of an approximate LD_{10} and histopatology assessment of a complete panel of tissues at a dose that causes toxicity.

2. A safe passage study in a non-rodent species that demonstrates that the mg/m^2 starting dose projected from the rodent study is not severely toxic when administered daily x 5. Note that this can be conducted in rabbits and can be a single dose group. Based on concerns about hepatotoxicity, we request that this

study include serum chemistry measurements in addition to clinical signs and mortality.

Until you have submitted the required information, and we notify you that you may initiate the trial, you may not legally conduct clinical studies under this IND.

Please identify your response to the clinical hold issues as a "CLINICAL HOLD COMPLETE RESPONSE." An incomplete response will not start the review clock. Your complete response submission should reference, by date, any information previously submitted necessary to fully respond to these clinical hold issues. To facilitate a response to your submission, submit this information in triplicate to the IND. In addition, send a copy of the cover letter to Ann Staten, Project Manager.

Following receipt of your complete response to these issues, we will notify you of our decision within 30 days.

In addition, we have the following recommendations and requests that are not clinical hold issues which may be addressed in your response to the clinical hold issues.

Clinical Deficiencies:

1. Safety would be enhanced if section 9.2.1 (p 16) of the protocol regarding the end of the accelerated phase, the statement beginning "Single patients are entered..." were amended to state that "standard phase will be initiated at first documentation of grade 2 or worse toxicity."

2. Given the reports of hepatotoxicity in animal studies, safety might be enhanced if bilirubin and transaminases were to be drawn weekly while on study and at termination.

Clinical Comments/Suggestions:

1. Safety might be enhanced if the protocol specified the maximum length of time patients are to be treated with stable disease.

2. The protocol (p.7) states that "patients will have an intravenous access device placed prior to starting therapy." If this access device is to be placed for the sole purpose of administering the study drug, this should be clearly stated in the consent form.

If we have additional comments or information requests not related to this clinical hold, we will notify you in approximately 30 days.

Correspondence to this IND can be sent to either of the following addresses:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
Division Document Room, HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
Division Document Room, HFD-150
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, contact Ann Staten, Regulatory Project Manager, at (301) 594-5770.

Sincerely yours,

Richard Pazdur MD

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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IND 58,915

Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, 10021

JAN 2 4 2000

Attention: Francis M. Sirotnak, Ph.D.

Dear Dr. Sirotnak:

Please refer to your Investigational New Drug Application (IND) submitted September 2, 1999, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for suberoylanilide hydroxamic acid (SAHA).

We also refer to your amendment dated December 29, 1999, serial number 002, which provided a complete response to our October 5, 1999 letter which cited the reasons for placing this IND on clinical hold and the information needed to resolve the clinical hold issues.

We have completed the review of your submission and have concluded that clinical trial may be initiated.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

All future communications regarding this IND should be forwarded in triplicate, identified with IND number 58,915 and addressed as follows:

(if via U.S. Postal Service)

FDA/CDER
Division of Oncology Drug Products,
HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

(if via courier)

FDA/CDER
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, contact Ann Staten, Regulatory Project Manager, at (301) 594-5770.

Sincerely yours,

Richard Pazdur MD

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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F.M. SIROTNAK

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